C.F.R. §§ 1.16 to 1.21 from Arnold, White & Durkee Deposit Account No. 01-2508/INGN:041/HYL.

In response to the restriction requirement which the Examiner imposed, Applicant elects, without traverse, to prosecute claims 1-20, *i.e.*, the Group I claims.

AMENDMENT

Please amend the application as follows:

In the claims:

1. (Amended) A method for treating a subject with a tumor comprising the steps of:

(a) providing an expression construct comprising a promoter functional in eukaryotic cells and a polynucleotide encoding a *p53* polypeptide, wherein said polynucleotide is positioned sense to and under the control of said promoter; and

(b) [contacting] administering said expression construct [with] to said tumor [cell] *in vivo*,

wherein said tumor comprises cells that express a functional *p53* polypeptide.

3. (Amended) The method of claim 1, wherein [the endogenous *p53* of] said tumor cell is [mutated] malignant.

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4. (Amended) The method of claim 1, wherein [the endogenous *p53* of] said tumor cell is [wild-type] benign.

11. (Amended) The method of claim 7, wherein [step (b) is repeated at least once] the expression ~~vector~~ construct is administered to said tumor at least a second time.

12. (Amended) The method of claim 11, wherein said tumor is resected following [a repeated contacting] at least a second administration, and an additional [contacting] administration is effected subsequent to [the] said resection.

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13. (Amended) The method of claim [12] 1, wherein said expression ~~vector~~ construct is [contacted] administered in a volume of about 3 ml. to about 10 ml.

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15. (Amended) The method of claim 1, wherein [said contacting is via intratumoral injection] the expression vector is administered.

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16. (Amended) The method of claim 1, wherein [said contacting is via injection] the expression construct is injected into a natural or artificial body cavity.

Please add the following new claims:

-- 26. (New) The method of claim 1, wherein [said contacting comprises multiple injections of] said tumor ~~is contacted with~~ said expression construct at least twice.

27. (New) The method of claim 26, wherein said multiple injections comprise about 0.1-0.5 ml volumes spaced about 1 cm apart.

28. (New) The method of claim 1, further comprising ~~contacting~~ said tumor with a DNA damaging agent.

29. (New) The method of claim 28, wherein said DNA damaging agent is a radiotherapeutic agent.

30. (New) The method of claim 29, wherein said radiotherapeutic agent is selected from the group consisting of γ-irradiation, x-irradiation, uv-irradiation and microwaves.

31. (New) The method of claim 28, wherein said DNA damaging agent is a chemotherapeutic agent.

32. (New) The method of claim 31, wherein said chemotherapeutic agent is selected from the group consisting of adriamycin, 5-fluorouracil, etoposide, camptothecin, actinomycin-D, mitomycin C, verapamil, doxorubicin, podophyllotoxin and cisplatin.

33. (New) The method of claim 1, further comprising contacting said tumor with a cytokine.

34. (New) The method of claim 1, further comprising contacting said tumor with a second therapeutic gene other than a gene encoding a *p53* polypeptide.

35. (New) The method of claim 34, wherein said second therapeutic gene is selected from the group consisting of a Dp gene, p21, p16, p27, E_2F, Rb, APC, DC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, FCC, MCC, *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl*, *abl*, Bax, Bcl-X_s and E1A.

36. (New) The method of claim 1, wherein said tumor is located ~~into~~ in a body cavity selected from the group consisting of the mouth, pharynx, esophagus, larynx, trachea, pleural cavity, peritoneal cavity, bladder interior and colon lumen.

37. (New) The method of claim 11, wherein [step (b) is repeated five times] ~~said tumor is contacted with said~~ is administered expression construct at least six times within a two week treatment regimen.

38. (New) A method for treating microscopic residual cancer comprising the steps of:

(i) identifying a patient having a resectable tumor;

(ii) resecting said tumor; and

(iii) contacting a tumor bed revealed by said resection with an expression construct comprising a promoter functional in eukaryotic cells and a polynucleotide encoding a *p53* polypeptide.

39. (New) The method of claim 38, wherein said resectable tumor is a squamous cell carcinoma.

40. (New) The method of claim 38, wherein the endogenous *p53* of said resectable tumor is mutated.

41. (New) The method of claim 38, wherein the endogenous *p53* of said resectable tumor is wild-type.

42. (New) The method of claim 38, wherein said expression construct is a viral vector.

43. (New) The method of claim 42, wherein said viral vector is selected from the group consisting of a retroviral vector, an adenoviral vector and an adeno-associated viral vector.

44. (New) The method of claim 43, wherein said adenoviral vector is a replication-deficient adenoviral vector.

45. (New) The method of claim 44, wherein said replication-deficient adenoviral vector is lacking at least a portion of the E1-region.

46. (New) The method of claim 38, wherein said promoter is a CMV IE promoter.

47. (New) The method of claim 38, wherein the resulting tumor bed is ~~contacted~~ administered with said expression construct at least twice.

48. (New) The method of claim 38, wherein said expression construct is ~~contacted with~~ administered to said tumor bed prior to closing of the incision.

49. (New) The method of claim 44, wherein said ~~the~~ tumor bed is ~~contacted~~ administered with from about 10^6 to about 10^9 infectious adenoviral particles.

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50. (New) The method of claim 47, further comprising ~~contacting said tumor with~~ administering said expression construct prior to resecting said tumor.

51. (New) The method of claim 50, wherein said tumor is injected with said expression construct.

52. (New) The method of claim 51, wherein said tumor is injected with about 10^6 to about 10^9 infectious adenoviral particles.

53. (New) The method of claim 51, wherein said tumor is injected with a total of about 1 ml to about 10 ml.

54. (New) The method of claim 51, wherein said tumor is injected at least twice.

55. (New) The method of claim 54, wherein each of said injections comprise about 0.1 ml to about 0.5 ml volumes spaced about 1 cm apart.

56. (New) The method of claim 38, wherein ~~the resulting tumor bed is contacted~~ is administered with said expression construct through a catheter.

57. (New) The method of claim 54, wherein said ~~contacting~~ administration comprises about 10^6 to about 10^9 infectious adenoviral particles.

58. (New) The method of claim 54, wherein said expression construct is ~~contacted with said tumor~~ administered in total of about 3 ml to about 10 ml.

59. (New) The method of claim 38, wherein the *p53* polynucleotide is tagged so that expression of a *p53* polypeptide can be detected.

60. (New) The method of claim 59, wherein the tag is a continuous epitope.

61. (New) The method of claim 38, further comprising contacting said tumor with a DNA damaging agent.

62. (New) The method of claim 61, wherein said DNA damaging agent is contacted before resection.

63. (New) The method of claim 61, wherein said DNA damaging agent is contacted after resection.

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64. (New) The method of claim 61, wherein said DNA damaging agent is contacted ~~contacting~~ before and after resection.

65. (New) The method of claim 61, wherein said DNA damaging agent is a radiotherapeutic agent.

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66. (New) The method of claim 65, wherein said radiotherapeutic agent is selected from the group consisting of γ-irradiation, x-irradiation, uv-irradiation and microwaves.

67. (New) The method of claim 61, wherein said DNA damaging agent is a chemotherapeutic agent.

68. (New) The method of claim 67, wherein said chemotherapeutic agent is selected from the group consisting of adriamycin, 5-fluorouracil, etoposide, camptothecin, actinomycin-D, mitomycin C, verapamil, doxorubicin, podophyllotoxin and cisplatin.

69. (New) The method of claim 38, further comprising contacting said tumor with a cytokine.

70. (New) The method of claim 69, wherein said cytokine is selected from the group consisting of IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, TGF-β, GM-CSF, M-CSF, TNFα, TNFβ, LAF, TCGF, BCGF, TRF, BAF, BDG, MP, LIF, OSM, TMF, PDGF, IFN-α, IFN-β and IFN-γ.

71. (New) The method of claim 38, further comprising contacting said tumor with a second therapeutic gene other than a gene encoding a *p53* polypeptide.

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72. (New) The method of claim 71, wherein said second therapeutic gene is selected from the group consisting of a Dp gene, p21, p16, p27, E_2F, Rb, APC, DC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, FCC, MCC, *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl*, *abl*, Bax, Bcl-X_s and E1A.

73. (New) The method of claim 38, wherein said tumor is located into a body cavity selected from the group consisting of the mouth, pharynx, esophagus, larynx, trachea, pleural cavity, peritoneal cavity, bladder interior and colon lumen.

74. (New) A method for treating a subject having a tumor comprising the steps of:

(i) surgically revealing said tumor; and

(ii) contacting said tumor with an expression construct comprising a promoter functional in eukaryotic cells and a polynucleotide encoding a *p53* polypeptide.

75. (New) The method of claim 74, wherein said tumor is malignant.

76. (New) The method of claim 74, wherein said tumor is a squamous cell carcinoma.

77. (New) The method of claim 74, wherein said tumor is benign.

78. (New) The method of claim 74, wherein the endogenous *p53* of said tumor is mutated.

79. (New) The method of claim 74, wherein the endogenous *p53* of said tumor is wild-type.

80. (New) The method of claim 74, wherein said expression construct is a viral vector.

81. (New) The method of claim 80, wherein said viral vector is selected from the group consisting of a retroviral vector, an adenoviral vector and an adeno-associated viral vector.

82. (New) The method of claim 81, wherein said adenoviral vector is a replication-deficient adenoviral vector.

83. (New) The method of claim 82, wherein said replication-deficient adenoviral vector is lacking at least a portion of the E1-region.

84. (New) The method of claim 74, wherein said promoter is a CMV IE promoter.

85. (New) The method of claim 74, wherein ~~said tumor is contacted with~~ is administered said expression construct at least twice.

86. (New) The method of claim 74, wherein said expression construct is ~~contacted with~~ administered said tumor prior to close of the incision.

87. (New) The method of claim 82, wherein said tumor is contacted with from about 10^6 to about 10^9 infectious adenoviral particles.

88. (New) The method of claim 74, wherein said tumor is contacted with said expression construct in a total of about 1 ml to about 10 ml.

89. (New) The method of claim 74, wherein said tumor is injected at least twice.

90. (New) The method of claim 89, wherein each of said injections comprise about 0.1 ml to about 0.5 ml volumes spaced about 1 cm apart.

91. (New) The method of claim 74, wherein ~~said tumor is contacted with~~ is administered said expression construct through a catheter.

92. (New) The method of claim 91, wherein said tumor is contacted with about 10^6 to about 10^9 infectious adenoviral particles.

93. (New) The method of claim 91, wherein said tumor is contacted with an expression construct in a total of about 3 ml to about 10 ml.

94. (New) The method of claim 74, wherein the *p53* polynucleotide is tagged so that expression of a *p53* polypeptide can be detected.

95. (New) The method of claim 94, wherein the tag is a continuous epitope.

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96. (New) The method of claim 74, further comprising contacting said tumor with a DNA damaging agent.

97. (New) The method of claim 96, wherein said DNA damaging agent is contacted with said tumor before resection.

98. (New) The method of claim 96, wherein said DNA damaging agent is contacted with said tumor after resection.

99. (New) The method of claim 96, wherein DNA damaging agent is contacted with said tumor before and after resection.

100. (New) The method of claim 96, wherein said DNA damaging agent is a radiotherapeutic agent.

101. (New) The method of claim 100, wherein said radiotherapeutic agent is selected from the group consisting of γ-irradiation, x-irradiation, uv-irradiation and microwaves.

102. (New) The method of claim 96, wherein said DNA damaging agent is a chemotherapeutic agent.

103. (New) The method of claim 102, wherein said chemotherapeutic agent is selected from the group consisting of adriamycin, 5-fluorouracil, etoposide, camptothecin, actinomycin-D, mitomycin C, verapamil, doxorubicin, podophyllotoxin and cisplatin.

104. (New) The method of claim 74, further comprising contacting said tumor with a cytokine.

105. (New) The method of claim 104, wherein said cytokine is selected from the group consisting of IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13,

TGF-β, GM-CSF, M-CSF, TNFα, TNFβ, LAF, TCGF, BCGF, TRF, BAF, BDG, MP, LIF, OSM, TMF, PDGF, IFN-α, IFN-β, and IFN-γ.

106. (New) The method of claim 74, further comprising contacting said tumor with a second therapeutic gene other than a gene encoding a *p53* polypeptide.

107. (New) The method of claim 106, wherein said second therapeutic gene is selected from the group consisting of a Dp gene, p21, p16, p27, E_2F, Rb, APC, DC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, FCC, MCC, *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl*, *abl*, Bax, Bcl-X_s and E1A.

108. (New) The method of claim 74, wherein said tumor is located in a body cavity selected from the group consisting of the mouth, pharynx, esophagus, larynx, trachea, pleural cavity, peritoneal cavity, bladder interior and colon lumen.

109. (New) A method for treating a subject having a tumor comprising the step of continuously perfusing a tumor site in said patient an expression construct comprising a promoter functional in eukaryotic cells and a polynucleotide encoding a *p53* polypeptide, wherein said polynucleotide is positioned sense to and under the control of said promoter.

110. (New) The method of claim 109, wherein said tumor is malignant.

111. (New) The method of claim 109, wherein said tumor is a squamous cell carcinoma.

112. (New) The method of claim 109, wherein said tumor is benign.

113. (New) The method of claim 109, wherein the endogenous *p53* of said tumor is mutated.

114. (New) The method of claim 109, wherein the endogenous *p53* of said tumor is wild-type.

115. (New) The method of claim 109, wherein said expression construct is a viral vector.

116. (New) The method of claim 115, wherein said viral vector is selected from the group consisting of a retroviral vector, an adenoviral vector and an adeno-associated viral vector.

117. (New) The method of claim 116, wherein said adenoviral vector is a replication-deficient adenoviral vector.

118. (New) The method of claim 117, wherein said replication-deficient adenoviral vector is lacking at least a portion of the E1-region.

119. (New) The method of claim 109, wherein said promoter is a CMV IE promoter.

120. (New) The method of claim 109, wherein said tumor site is perfused from about one to two hours.

121. (New) The method of claim 109, wherein said subject is a human.

122. (New) The method of claim 109, wherein said tumor site is contacted with said expression vector through a catheter.

123. (New) The method of claim 109, wherein the *p53* polynucleotide is tagged so that expression of a *p53* polypeptide can be detected.

124. (New) The method of claim 123, wherein the tag is a continuous epitope.

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125. (New) The method of claim 109, further comprising contacting said tumor with a DNA damaging agent.

126. (New) The method of claim 125, wherein said tumor site is contacted with said DNA damaging agent before resection.

127. (New) The method of claim 125, wherein said tumor site is contacted with said DNA damaging agent after resection.

128. (New) The method of claim 125, wherein said tumor site is contacted with said DNA damaging agent before and after resection.

129. (New) The method of claim 125, wherein said DNA damaging agent is a radiotherapeutic agent.

130. (New) The method of claim 129, wherein said radiotherapeutic agent is selected from the group consisting of γ-irradiation, x-irradiation, uv-irradiation and microwaves.

131. (New) The method of claim 125, wherein said DNA damaging agent is a chemotherapeutic agent.

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132. (New) The method of claim 131, wherein said chemotherapeutic agent is selected from the group consisting of adriamycin, 5-fluorouracil, etoposide, camptothecin, actinomycin-D, mitomycin C, verapamil, doxorubicin, podophyllotoxin and cisplatin.

133. (New) The method of claim 109, further comprising contacting said tumor with a cytokine.

134. (New) The method of claim 133, wherein said cytokine is selected from the group consisting of IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13,

TGF-β, GM-CSF, M-CSF, TNFα, TNFβ, LAF, TCGF, BCGF, TRF, BAF, BDG, MP, LIF, OSM, TMF, PDGF, IFN-α, IFN-β, and IFN-γ.

135. (New) The method of claim 74, further comprising contacting said tumor with a second therapeutic gene other than a gene encoding a *p53* polypeptide.

136. (New) The method of claim 135, wherein said second therapeutic gene is selected from the group consisting of a Dp gene, p21, p16, p27, E_2F, Rb, APC, DC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, FCC, MCC, *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl*, *abl*, Bax, Bcl-X_s and E1A.

137. (New) The method of claim 109, wherein said tumor is located into a body cavity selected from the group consisting of the mouth, pharynx, esophagus, larynx, trachea, pleural cavity, peritoneal cavity, bladder interior and colon lumen. --

A fee as set forth in 37 C.F.R. §§ 1.16-1.21 in the amount of $1418.00 is enclosed herewith. If an appropriate check has not been enclosed, or if it is insufficient under 37 C.F.R §§ 1.16 to 1.21, the Commissioner is hereby authorized to deduct any necessary fees from Arnold, White & Durkee Deposit Account No. 01-2508/INGN:041/HYL.

The Examiner is invited to contact the undersigned attorney at (512) 418-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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